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CHRONIC PELVIC PAIN OF BLADDER ORIGIN:

A Focus on Interstitial Cystitis

Case Studies

PRESENTED BY

U.S. Department of Health and Human Services

The Office on Women's Health

IN COOPERATION WITH

American Medical Women's Association

American Urogynecologic Society

National Association of Nurse Practitioners in Women's Health

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STATEMENT OF NEED

Interstitial cystitis is commonly misdiagnosed in women as overactive bladder, recurrent urinary tract infection, or endometriosis; in men it is often mistaken for prostatitis. The impact of interstitial cystitis on a patient's quality-of-life is significant — these women score lower on QOL inventories than do dialysis patients; in men, the impact is comparable to that of patients with myocardial infarction, angina, or Crohn's disease. Therefore, effective diagnostic methods, understanding of epidemiology and demographics, and proper identification of nonpharmacologic and pharmacologic options are necessary for the management of interstitial cystitis.

METHOD OF PARTICIPATION

This newsletter should take approximately 1 hour to complete. The participant should, in order, read the objectives and newsletter, answer the 10-question multiple-choice post-test, placing answers on the Registration/Posttest Answer Form/Evaluation on page 6. The evaluation form provides each participant with the opportunity to comment on the quality of the instructional process, the perception of enhanced professional effectiveness, the perception of commercial bias, and his or her views on future educational needs. To receive credit for this activity, follow the instructions provided on the posttest and evaluation form. This credit will be valid through November 30, 2005. No credit will be given after that date.

EDUCATIONAL OBJECTIVES

Upon completion of this program, participants will be able to:

- Differentiate between chronic pain of pelvic origin versus bladder origin
- Discuss the epidemiology and demographics of chronic pelvic pain and interstitial cystitis
- Discuss the current theories regarding the underlying pathophysiology of interstitial cystitis
- Discuss the impact of interstitial cystitis and chronic pelvic pain on quality of life
- Describe the evolving role of the Pelvic Pain Urgency and Frequency Patient Symptom Scale, Potassium Sensitivity Test, and other diagnostic tools in identifying patients with interstitial cystitis
- Identify nonpharmacologic and pharmacologic options for the management of interstitial cystitis

TARGET AUDIENCE

Obstetrician/gynecologists, urologists, family physicians, nurse practitioners, and physician assistants.

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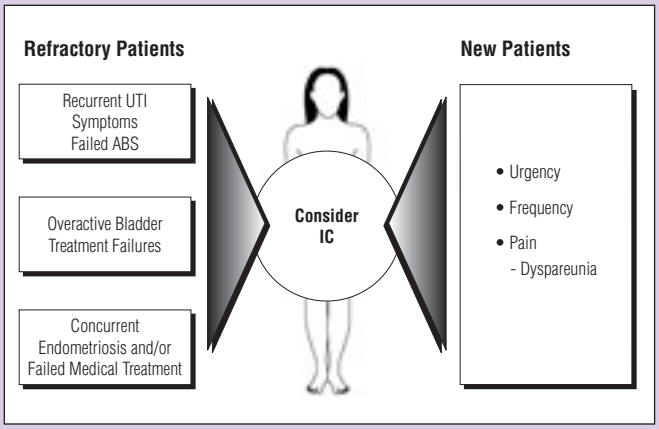
CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS CASE STUDIES

INTRODUCTION

Interstitial cystitis (IC) causes the symptoms of a chronic pelvic pain syndrome (CPPS) of bladder origin that is estimated to affect as many as 1 in 4.5 women.[1] IC causes the symptoms of chronic pelvic pain (CPP) and urinary urgency and frequency, but is frequently misdiagnosed as endometriosis, recurrent urinary tract infection (UTI), or overactive bladder (OAB) (Figure 1). During this past decade there has been a greater understanding of the probable underlying pathophysiology of IC, as well as significant advances in the diagnosis and management of this cause of CPPS. Consequently, clinicians now have techniques to identify and effectively treat women with IC early in the process of this disease.

FIGURE 1

HOW TO CONSIDER AN IC PATIENT



This is the second of 2 issues of *Clinical Courier*® that will focus on the assessment and management of IC in women. The objective of this activity is to provide practical information and guidelines that can be utilized to expedite the care provided to patients who experience symptoms of CPP that are eventually determined to be of bladder origin. The first issue examined 2 cases of IC that were initially diagnosed as endometriosis. In this issue, 2 case studies of women with bladder-related diagnoses will be presented and reviewed.

OVERVIEW AND MAGNITUDE OF THE PROBLEM

In March 2004, the American College of Obstetricians and Gynecologists (ACOG) issued a Practice Bulletin about CPP, which was defined as "noncyclic pain of 6 or more months' duration that localizes to the anatomic pelvis, abdominal wall at or below the umbilicus, lumbosacral back, or the buttocks and is of sufficient severity to cause functional disability or lead to medical care."[2] The origin of the pain can be genitourinary, gastrointestinal, reproductive, psychologic, or neurologic. It was noted that the severity of the pain is not necessarily associated with physical findings.

A common cause of CPP is IC, described by ACOG as a "chronic inflammatory condition of the bladder characterized by irritative voiding symptoms of urgency and frequency in the absence of objective evidence of another disease that could cause the symptoms."[2] IC symptoms can range from mild and intermittent pelvic pain with infrequent nighttime nocturia (≤ 2 times per night) to debilitating pain and frequent nighttime nocturia (>12 times per night). Although the exact incidence of IC is unknown, the ACOG Practice Bulletin estimated that 38% to 85% of women seeking gynecologic care for CPP may have IC.[2] A recent study suggested that as many as 1 in 4.5 women has IC.[1]

IC is most typically diagnosed in white women of reproductive age. While the majority of women first notice symptoms of IC during their 30s, there is usually a delay of 5 to 8 years before an accurate diagnosis is established, resulting in an age range at diagnosis of 42 to 46 years.[3,4] Women consult an average of 5 to 8 healthcare professionals before receiving the correct diagnosis of IC; this problem has been attributed to a lack of understanding that the bladder is a common source of pelvic pain and the fact that there are many similarities in the clinical presentations of IC and endometriosis, UTI, and OAB.[3] Women with any of the causes of CPPS can experience dyspareunia, premenstrual flares, and diet-related exacerbations, further confounding the ability to make a correct diagnosis.

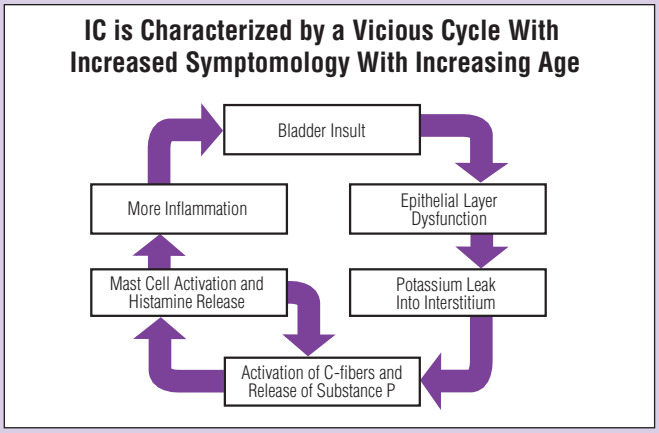
PATHOPHYSIOLOGY

Currently there are 3 main components of the pathogenesis of IC, and all of these components may occur in the same patient. The predominant etiologic factor is based upon the belief that patients with IC have an elevated pain response to urine solutes because of damage to the glycosaminoglycan (GAG) layer of the bladder surface. This damage results in leakage and transvesical absorption of urea and potassium into the interstitium of the bladder. In a healthy bladder, the GAG layer (mucus) prevents absorption of caustic components of urine into the bladder wall and inhibits bladder infections by preventing bacteria from adhering to urothelial surfaces. Trauma to, or a deficiency in, the GAG layer results in bladder wall exposure to potassium, resulting in tissue damage and pain, as well as urinary urgency and frequency, which are characteristic of IC.[5] However, pain can also occur in the absence of actual tissue damage.

In addition to damage or alterations to the GAG layer, it is also believed that when IC is present in the bladder wall there is neurogenic inflammation with activation of C-fibers and the release of the neuropeptic substance P (SP), as well as increased mast cell activation. Patients with IC have an increased number of C-fibers (pain-carrying nerves) that carry and release SP from sensory nerve endings. SP transmits pain information, stimulates inflammation, and can trigger mast-cell secretion, especially in the bladder submucosa.[6] Mast cells are located predominantly in the detrusor layer, in the lamina propia, and the bladder epithelium. Inside mast cells are granules that contain histamines; when the mast cells degranulate, histamines are abnormally released, causing inflammation. It has been hypothesized that this process may be responsible for the initial insult or damage to the GAG layer. In summary, the pathogenesis of IC appears to be a vicious cycle involving depletion of the GAG layer, mast cell activation with histamine release, and C-fiber activation and release of SP (Figure 2).[7] The epithelial dysfunction can affect tissue beyond the bladder wall; therefore, IC is not an end-organ disease but a visceral pain syndrome with neuropathic up-regulation as a key component.

FIGURE 2

PATHOGENESIS OF IC[7]



Adapted with permission from Evans RJ. *Rev Urol.* 2002;4(suppl 1):S16-S20.

DIAGNOSIS

The diagnosis of IC is a clinical process. There are no gross histologic changes associated with IC, nor are there, as yet, laboratory assays or biomarkers to assist in establishing the diagnosis. IC has been a diagnosis of exclusion, ruling out infection (UTI or bladder, vaginal, or sexually transmitted), endometriosis, and bladder cancer. It was originally believed that the diagnosis of IC could be made only when Hunner's ulcers, observed through cystoscopy with hydrodistention, were present. However, recent studies have reported that fewer than 10% of patients with IC have a Hunner's ulcer.[8] Consequently, the diagnosis depends upon patient history, presenting signs and symptoms, and negative laboratory results (negative urinalysis, sterile urine culture, and normal urinary cytology) (Table 1). It is the recommendation of the editorial faculty performing cystoscopy with hydrodistention is currently recommended only for women with gross or microscopic hematuria to rule out abnormalities of the urethral or bladder surface, or for older women who smoke and have other risk factors for bladder cancer. In summary, IC should be suspected to be present in all women with CPP and urinary urgency/frequency in the absence of observed pathologic changes – including women with refractory UTI who have failed antibiotics, women with refractory OAB who have failed anticholinergic treatment, and women with persistent symptoms of endometriosis who have not responded to the usual medical and surgical therapies.

TABLE 1

DIAGNOSIS OF IC

Patient History + Clinical Presentation
Urinalysis and Culture
Bladder Cytology
Voiding Log
Physical Exam
PUF Patient Symptom Scale
PST – as appropriate
Cystoscopy With Hydrodistention - only if gross/ microscopic hematuria is present

Women with IC frequently have suprapubic tenderness, anterior vaginal wall/bladder base tenderness, and/or rectal or levator muscle spasm during a physical examination. The physical exam can rule out vaginitis, vulvodynia, urethral diverticula, uterovaginal prolapse, and pelvic floor dysfunction. Complaints of pelvic pain are common, especially as the disease progresses. The pain can be referred to the urethra, vagina, lower abdomen, lower back, medial aspect of the thigh, inguinal region, or vulva. Some women may require additional diagnostic tests, such as an intravenous pyelogram, transvaginal ultrasound, and cystometrogram with uroflow examination. Women often report that emotional or physical stress, certain foods, and seasonal allergies exacerbate their IC symptoms.

Two recent additions to the diagnostic armamentarium include the Pelvic Pain Urgency and Frequency (PUF) Patient Symptom Scale and the Potassium Sensitivity Test (PST). The PUF is an 8-question symptom scale that can be completed in the office in approximately 5 minutes; it quantifies the presence and severity of the symptoms of frequency, urgency, and pain, and includes 2 questions assessing symptoms following sexual activity (Figure 3, page 6). The maximum score on the PUF is 35 points; a high score, which is considered to be ≥10 points, indicates a high probability that the patient has IC. Nearly all healthy women have low PUF scores (≤2 points). The PUF has been shown to readily distinguish IC from other abdomenopelvic conditions, including UTI and gynecologic CPP. Patients with PUF scores >10 points have been shown to have a 74% likelihood of IC.[1] Further, patients with PUF scores of 5 to 10 points have been shown to have a 55% likelihood of IC. It is recommended that the PUF scale should be routinely applied to all women with CPP, and women with a PUF score of ≥5 points should be suspected of having IC and managed accordingly.

The second advancement in the IC diagnostic process is the PST, a test that identifies patients who respond with pain and/or urgency to the introduction of a potassium solution into the bladder. Approximately 80% of patients with IC have a positive PST result.[9] It should be noted that a positive PST occurs when there is abnormal epithelial permeability, so other diseases with the symptom of an abnormal mucosa will also cause a positive PST, for example, acute bacterial cystitis and radiation cystitis. Similarly, a negative PST does not always rule out IC. Women who have recently undergone hydrodistention, heparin treatment, or bladder instillation of dimethyl sulfoxide (DMSO), or patients taking pain medication can have false negative results. Nevertheless — and often with alternative initial diagnoses—approximately 85% of gynecology patients with CPP have a positive PST.[1,10]

The PST involves the very slow introduction into the bladder of 2 separate solutions through a thin catheter. First, 40 mL of room temperature sterile

water is slowly instilled to assess the patient's baseline of pain perception and urgency upon bladder filling. The patient is asked to rate this experience using a 0- to 5-point scale, with 5 indicating the most severe pain. The water should be retained in the bladder for about 5 minutes before it is emptied through the catheter. Then, 40 mL of a potassium chloride (KCl) solution is instilled and retained for up to 5 minutes; the patient then evaluates the severity of pain/urgency with the KCl. Any increase of 2 or more points over the baseline point with sterile water indicates a positive PST result. Less than a 2 point difference in pain or urgency with the KCl solution compared with the sterile water solution is considered a negative PST result. Women who do not initially respond to the KCl instillation but who have other signs and symptoms of IC should have the catheter removed and the bladder emptied, after which a second KCl solution is instilled.

There is a strong correlation between a positive PST result and high PUF scores.[1] Ninety-one percent of patients with a PUF score >20 have a positive PST, as do 76% of patients with a PUF score of 15 to 19 and 55% of patients with a PUF score of 5 to 9.[1] Healthy women usually have 0% positive PST results and PUF scores <2. The high correlation between the PUF and PST suggests that the PUF can be used as an initial diagnostic screening test to identify women with CPP who are highly likely to have IC, reserving the PST for women whose symptoms are suggestive of IC but who have lower PUF scores (5 to 10 points).

MANAGEMENT

Until the approval by the US Food and Drug Administration (FDA) of oral pentosan polysulfate sodium (PPS), intravesical instillation with DMSO was the only therapy indicated for the management of IC. Intravesical instillation with DMSO provides moderate relief of the pain and urinary symptoms of IC.[11-14] The procedure involves passing 50 mL of a 50% aqueous solution of DMSO through a catheter into the bladder, where it is retained for up to 15 minutes before being expelled.[14,15] DMSO instillations can be performed in the office or at home by the patient on a weekly or biweekly schedule for a treatment course of 6 to 8 weeks. The procedure can be painful, and the process can leave a garlic-like taste and/or odor on the breath or skin for up to 3 days after treatment.[15] The mechanism of action is as yet unknown. Patients receiving DMSO instillations are advised to undergo blood and eye testing, including kidney and liver function tests, every 6 months.[16] Symptoms often recur after treatment with DMSO, and additional courses of therapy are needed to ensure duration of remissions.[17] DMSO therapy is being used less frequently now than previously.

PPS is the only oral drug approved by the FDA for the management of the pain and urinary symptoms of IC.[18] PPS is a heparin-like compound similar in chemistry and structure to the naturally occurring GAGs that overlie the urinary epithelium (Table 2).[18-23] It is believed that PPS acts by gradually and methodically repairing the defective GAG layer, thus providing a buffer to control cell permeability and preventing irritating solutes from reaching uroepithelial cells.

The FDA-recommended dosage of oral PPS is 300 mg/d taken as a 100-mg capsule 3 times daily; an evolving regimen to enhance patient compliance utilizes 200 mg taken twice daily.[24,25] The recommended course duration is 2 to 4 months for women with mild disease, and 6 to 12 months or more for women with moderate to severe disease, as there is a long duration between initiation of therapy and relief of symptoms.[20] PPS is a well-tolerated agent with no known drug-drug interactions.[18]

The efficacy of PPS for reducing the symptoms of IC has been demonstrated in numerous clinical trials.[22,26,27] PPS reduces the pelvic pain and pressure to void, and has been shown to increase bladder capacity (volume per void). PPS also significantly reduces potassium sensitivity as measured by the PST.[28] Finally, a dose ranging study demonstrated that symptomatic improvement increased with duration of therapy but not with increased dosage (Figure 4).[28]

A wide range of adjunctive pharmacologic and nonpharmacologic therapies can be used to augment the primary treatment of IC. Analgesics, including acetaminophen with codeine, can provide pain relief. Anticholinergics and antispasmodics are recommended for patients with OAB symptoms, and antihistamines are recommended for patients with allergic flares. Tricyclic antidepressants, particularly amitriptyline, are often recommended at bedtime to promote pain relief. Amitriptyline also inhibits histamine secretion from mast cells. Because this agent can cause constipation and cardiac irregularities, treatment with amitriptyline should be initiated at the lowest dosage and slowly titrated up to the dose that provides the greatest symptom relief without adverse effects.[29] Although not approved by the FDA for IC, intravesical instillation of a heparin solution has been used as monotherapy and in combination with DMSO to provide prompt relief of pain and to enhance the duration of clinical remissions.[30,31]

A unique intervention for women with severe IC symptoms is an anesthetic intravesical "rescue" solution (not FDA approved). The anesthetic solution provides immediate, although temporary, relief of urgency and pain symptoms. These "therapeutic cocktails" are composed of either PPS (1 or 2 100-mg capsules dissolved in 10 cc of buffered normal saline or heparin (10,000 to

TABLE 2

PENTOSAN POLYSULFATE SODIUM

The only FDA-approved oral therapy for management of IC

Proven effective in multicenter randomized trials with placebo[19,20]

Resembles protective GAG layer that insulates bladder lining against urine[21]

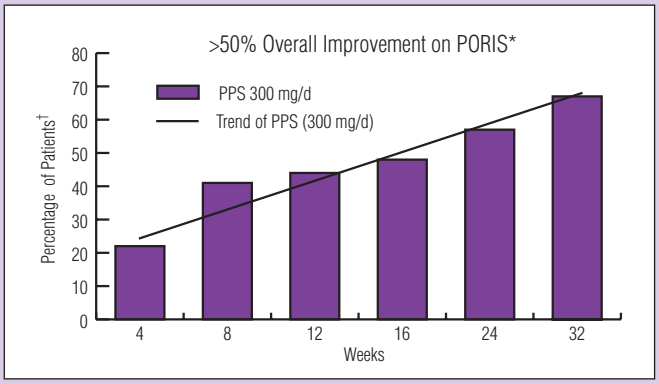
Reduces painful symptoms/provides long-term remissions[22]

Provides relief of IC pain in many patients in 3 to 6 months[18]

Some patients experience pain relief in only 4 weeks[23]

FIGURE 4

PPS SYMPTOMATIC IMPROVEMENT INCREASES WITH DURATION OF TREATMENT[28]



*PORIS = Patient's Overall Rating of Improvement of Symptoms index assessing, pain, urgency, frequency, and nocturia.

†Completers.

40,000 units) as the active agent in combination with 3 cc of 8.4% sodium bicarbonate and 10 cc of 1% lidocaine or 16 cc of 2% lidocaine.[30,32,33] The solution is instilled into an empty bladder using a small catheter while the woman assumes a dorsal lithotomy position. The solution is held in the bladder for up to 30 minutes or until the patient needs to void. Clinical investigators suggest a series of 9 anesthetic solutions (3 per week for 3 weeks, or 3 during the first week and 1 per week for the next 6 weeks) to provide maximal pain relief and to facilitate reductions in urinary urgency. This regimen may be continued for additional weeks if needed.

Nonpharmacologic interventions are rarely sufficient as monotherapy for IC. The most common nonpharmacologic interventions include diet modification, bladder-training techniques (often in conjunction with relaxation and distraction techniques) to increase the interval between voids, and pelvic floor relaxation exercises. Anecdotal reports indicate that avoiding foods high in acidity and those containing caffeine, potassium, or artificial sweeteners can have a beneficial effect on IC pain. Behavioral therapies such as bladder-training techniques, are most effective for women with mild-to-moderate IC, but can also be of benefit to women with more severe symptoms. Other recommendations include taking hot sitz baths and applying a heating pad to the perineal area prior to, and ice packs after, sexual intercourse.

CASE STUDY

Case Study 1: The Patient With Recurrent UTI

A 25-year old white female was treated 12 times in 2 years for UTI prior to referral. She presented with symptoms of urinary frequency, pelvic pain, and dyspareunia.

History of Present Illness

Patient 1 had a 2-year history of treatment for recurrent UTI-type symptoms, including 12 courses of antimicrobial agents (including trimethoprim sulfamethoxazole, nitrofurantoin monohydrate/macrocrystals, ciprofloxacin, and levofloxacin) and 2 urethral dilatation procedures. Most of the treatments had been initiated after phone triage—her urine was examined only once during the 2 years. Her complaints of dyspareunia and chronic pelvic pain were regarded as related to the presumptive UTI diagnosis.

During the initial visit, Patient 1 complained of urinary frequency and suprapubic pain and tenderness during intercourse. She reported that she was in a long-term, monogamous relationship but was afraid to commit to marriage as her problem with painful intercourse was worsening. She noted that her fiancé felt she was "obsessed" with her bladder after she admitted to him that she voided 18 to 20 times per day. Patient 1 also noted that she awoke 3 to 5 times each night to void.

Physical Examination and Laboratory Findings

Laboratory testing on Patient 1 found no urinary tract infection: results showed a negative urinalysis, sterile culture, and normal cytology. There was no evidence of vaginitis or sexually transmitted infection. Physical examination demonstrated suprapubic and perineal tenderness and bladder base tenderness.

Current Diagnostic Assessment

Patient 1 was given the PUF Patient Symptom Scale and scored 18. The clinician chose not to perform a PST. Cystoscopy with hydrodistention was not indicated because the patient had no risk factors for bladder cancer (she did not smoke and was young) and had no gross or microscopic hematuria.

Short-Term Treatment Plan

Patient 1 was given a presumptive diagnosis of IC and was placed on oral PPS (300 mg/d) and amitriptyline (25 mg at bedtime) (not indicated for IC). She was also started on an "IC diet," on which she eliminated foods that contain caffeine, potassium, acidity, or artificial sweeteners, and began a pelvic muscle rehabilitation program with biofeedback. After 2 weeks of treatment, she reported good improvement in the pain and bladder symptoms; within 6 weeks of treatment initiation, she was having intercourse without pain.

Follow-Up

Patient 1 was seen on a monthly basis for the first year after being diagnosed with IC, and every 6 months thereafter. She was able to stop the amitriptyline after 8 months. She chose not to discontinue taking oral PPS, after a short trial without it caused a recurrence of pain and discomfort. She married her fiancé and became pregnant with her first child. Because PPS is a class B drug, the patient chose to continue taking it throughout her pregnancy. She adhered to a strict "IC diet" for 12 months, but eventually was able to return to a less restricted diet. She will continue to be seen every 6 months for management of IC after she has delivered her child.

Discussion

Women are frequently treated empirically for UTI without ever obtaining confirmation of a bacterial etiology. It is therefore common for women to receive numerous courses of antimicrobial therapy, often with different antimicrobial agents, without experiencing significant improvement in their CPP and bladder symptomatology.

Case Study 2: The Patient Misdiagnosed With OAB

A 32-year old lawyer has been treated by her family physician for OAB for the past 4 years. She complains of urinary frequency and urgency, reduced urinary output, and pelvic pain.

History of Present Illness

Patient 2 has been treated for OAB for the past 4 years with antimuscarinic agents, such as oxybutynin and tolterodine. These agents do not appear to be of benefit—in fact, she reports increasing pain and urinary retention. She has no history of UTI or treatment for UTI, and no history of involuntary leakage of urine. The increased number of voiding episodes and pelvic pain was interfering with her ability to work, and she noted that her social life was suffering because of these symptoms.

Physical Examination and Laboratory Findings

Patient 2 was asked to keep a voiding/bladder diary for 1 week, and to record the volume of urine for each voiding episode. The voiding log demonstrated that she was voiding 1 to 2 times per hour, with an average voided volume of 20 to 40 mL per void. She reported considerable pain when the void volume was ≥90 mL. On examination, her urine was clear with minimal postvoid residual urine. Pelvic examination found suprapubic tenderness to be present.

Current Diagnostic Assessment

The PUF was administered and Patient 2 scored 20. Her high PUF score, in addition to her history, negative laboratory findings, and clinical presentation suggested a presumptive diagnosis of IC. It was decided that the PST and cystoscopy with hydrodistention procedures were unnecessary at this time.

Short-Term Treatment Plan

Patient 2 was directed to stop taking the antimuscarinics. Oral PPS (300 mg/d) was initially prescribed. She was given a series of 9 intravesical anesthetic solutions over a 7-week period. She received instructions for bladder training techniques, where she learned to schedule her voids with the short-term goal (3 months) of voiding once every 3 hours. She was given written instructions regarding the "IC diet."

Follow-Up

Patient 2 returned for follow-up at 3 months, 6 months, and 1 year after initiation of treatment. At 3 months, she reported a reduction in her pelvic pain, and her interval between voids had increased to nearly 2 hours. Her average voided volume had also increased, and she no longer reported significant discomfort

with larger voided volumes. She continued taking oral PPS for a total of 9 months, and was symptom-free by 1 year after initiation of treatment.

Discussion

Patient 2 was initially diagnosed with OAB and treated with antimuscarinic agents that did not address her underlying IC. While antimuscarinic agents may be of benefit to a small subset of women with IC, these drugs treat only the symptoms and not the disease process. Antimuscarinic agents should be used carefully as they can increase the pelvic pain and lead to urinary retention in some women.

CONCLUSIONS

IC is frequently misdiagnosed as either OAB or UTI, especially when no laboratory analyses are performed. All 3 conditions have similar presentations of pelvic pain with urinary urgency and frequency, but only UTIs have a bacterial etiology. It is therefore important for all women with this clinical presentation and absence of definitive pathology to be screened for IC using the PUF; women who score ≥5 points should be considered to have IC that should be addressed and treated accordingly.

REFERENCES

1. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002;60:573-578.
2. ACOG Committee on Practice Bulletins - Gynecology. ACOG Practice Bulletin No. 51. Chronic pelvic pain. *Obstet Gynecol* 2004;103:589-605.
3. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. *J Urol* 1999;161:549-552.
4. Propert KJ, Schaeffer AJ, Brensinger CM, et al. A prospective study of interstitial cystitis: results of longitudinal followup of the interstitial cystitis data base cohort. The Interstitial Cystitis Data Base Study Group. *J Urol* 2000;163:1434-1439.
5. Parsons CL, Greenberger M, Gabal L, Bidair M, Barme G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998;159:1862-1866.
6. Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibres in interstitial cystitis. *Br J Urol* 1995;75:744-750.
7. Evans R. Treatment approaches for interstitial cystitis: multimodal therapy. *Rev Urol* 2002;4:S16-S20.
8. Nigro DA, Wein AJ, Foy M, et al. Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. *Urology* 1997;49:86-92.
9. Parsons CL. Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. *Urology* 2003; 62:976-982.
10. Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ. Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity. *Obstet Gynecol* 2001;98:127-132.
11. Stewart BH, Shirley SW. Further experience with intravesical dimethyl sulfoxide in the treatment of interstitial cystitis. *J Urol* 1976;116:36-38.
12. Stout L, Gerspach JM, Levy SM, et al. Dimethyl sulfoxide does not trigger urine histamine release in interstitial cystitis. *Urology* 1995;46:653-656.
13. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol* 1988;140:36-39.
14. Barker SB, Matthews PN, Philip PF, Williams G. Prospective study of intravesical dimethyl sulphoxide in the treatment of chronic inflammatory bladder disease. *Br J Urol* 1987;59:142-144.
15. Sant GR. Intravesical 50% dimethyl sulfoxide (Rimso-50) in treatment of interstitial cystitis. *Urology* 1987;29:17-21.
16. RIMSO-50®. Physicians' Desk Reference®. Montvale, NJ: Thomson PDR; 2004. p. 1215.
17. Ghoniem GM, McBride D, Sood OP, Lewis V. Clinical experience with multiagent intravesical therapy in interstitial cystitis patients unresponsive to single-agent therapy. *World J Urol* 1993;11:178-182.
18. Elmiron®. Physicians' Desk Reference®. 58th ed. Montvale, NJ: Thomson PDR; 2004. p. 2438-2439.
19. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. *Urol Clin North Am* 1994;21:93-100.
20. Parsons CL, Benson G, Childs SJ, et al. A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentosan polysulfate. *J Urol* 1993;150:845-848.
21. Hurst R, Roy J, Min K, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. *Urology* 1996; 48:817-821.
22. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology* 1997;49:93-99.
23. Nickel JC, Forrest J, Barkin J, Payne C, Mosbaugh P. Safety and efficacy of up to 900 mg/day polysulfate sodium (Elmiron) in patients with interstitial cystitis. *Urology* 2001;57:122-123.
24. Dell J, Parsons C. Intravesical instillation therapy using PPS in patients with interstitial cystitis. Poster presented at: Research Insights into Interstitial Cystitis. Alexandria, Virginia; October 30-November 1, 2003.
25. Rosenberg M, Page S, Roth L, al. e. Pentosan polysulfate sodium for the treatment of interstitial cystitis: Rapid (1-month) and sustained symptom relief. Paper presented at: Research Insights into Interstitial Cystitis (A Basic and Clinical Science Symposium), October 30-November 1, 2003; Alexandria, Virginia.
26. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosan polysulfate. *J Urol* 1987;138:513-516.
27. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis. A double-blind placebo-controlled clinical study. *Urology* 1990;35:552-558.
28. Parsons CL, Forrest J, Nickel JC, et al. Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. *Urology* 2002;59:329-333.
29. Hanno PM. Amitriptyline in the treatment of interstitial cystitis. *Urol Clin North Am* 1994;21:89-91.
30. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol* 1994;73:504-507.
31. Kuo HC. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. *J Formos Med Assoc* 2001;100:309-314.
32. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ. A placebo-controlled study of intravesical pentosan polysulfate for the treatment of interstitial cystitis. *Br J Urol* 1997;79:168-171.
33. Parsons CL, Davis EL. Pentosan polysulfate sodium intravesical instillation: end-organ therapy. *Practice Building Today.* September 2003:18-22.

FIGURE 3

PELVIC PAIN AND URGENCY/FREQUENCY (PUF) PATIENT SYMPTOM SCALE

Patient's Name:_____ Today's date: _____

Please circle the answer that best describes how you feel for each question.

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom, does it bother you?	Never bothers	Occasionally	Usually	Always			
3	Are you currently sexually active? YES _____ NO _____							
4	**a. IF YOU ARE SEXUALLY ACTIVE,** do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always			
	b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
7	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
8	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
							SYMPTOM SCORE (1, 2a, 4a, 5, 6a, 7, 8a)	
							BOTHER SCORE (2b, 4b, 6b, 8b)	
							TOTAL SCORE (Symptom Score + Bother Score) =	

Total score ranges are from 1 to 35.
A total score of 10-14 = 74% likelihood of positive PST; 15-19 = 76%; 20+ = 91% Potassium Positive

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IMPORTANT CME MATERIALS ENCLOSED

CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS CASE STUDIES

CME POSTTEST/REGISTRATION/EVALUATION (04-726D)

Release date: November 2004
Expiration Date for credit: November 30, 2005

Instructions:
Please mark your answers on the Posttest Answer Form below.

This activity should take approximately 1 hour to complete. The participant should, in order, read the educational objectives contained in this newsletter, answer the 10-question multiple-choice posttest, below, and complete the registration/evaluation form. If you wish to receive CME credit and a certificate, please mail/fax a copy of your completed answers to:

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Attention: 04-726D
5711 Northwest Parkway, Suite 100, San Antonio, TX 78249-3360
Fax (210) 697-9318 Phone: (800) 328-2308

Expiration date for credit: November 30, 2005

POSTTEST/SELF ASSESSMENT (Circle the single most appropriate answer below.)

1. IC is frequently misdiagnosed in women as:
   a. CPP due to abdominopelvic adhesions
   b. Vulvar dermatitis
   c. Recurrent UTI or OAB
   d. Pelvic inflammatory disease

2. The average age of IC diagnosis is:
   a. 23 - 26 years
   b. 29 - 35 years
   c. 36-41 years
   d. 42-46 years

3. The pain and urinary symptoms that characterize IC are most probably caused by:
   a. The presence of unusual organisms in bladder cells
   b. Damage to the GAG layer allowing bladder wall exposure to potassium
   c. Autoimmune processes
   d. All of the above

4. A PST should be performed on:
   a. All women with a history and clinical presentation suggestive of IC
   b. Women with suspected IC and a PUF score >10
   c. Women with suspected IC and a PUF score between 5-10
   d. All women who present with CPP

5. The PUF test measures:
   a. Epithelial permeability
   b. Bladder capacity
   c. The presence and severity of IC symptoms
   d. All of the above

6. The recommended course duration for treatment of moderate to severe IC with oral PPS is:
   a. 1 to 2 months
   b. 3 to 4 months
   c. 4 to 6 months
   d. 6 to 12 months

7. PPS is believed to act by:
   a. Preventing irritating solutes from reaching epithelial cells
   b. Providing a buffer to control cell permeability
   c. Replenishing the defective GAG layer
   d. All of the above

8. Which of the following is recommended for short-duration use to supplement oral PPS in women with severe IC?
   a. Intravesical instillations with DMSO
   b. Intravesical instillations with heparin
   c. Intravesical instillations with anesthetic rescue solutions
   d. Bladder training techniques

9. Women with IC will demonstrate which of the following during a pelvic examination?
   a. Perineal tenderness
   b. Suprapubic tenderness
   c. Bladder base tenderness
   d. All of the above
   e. None of the above

10. IC should be suspected in women with:
    a. Recurrent UTIs
    b. Recalcitrant OAB
    c. History or suspicion of endometriosis
    d. All of the above

PROGRAM EVALUATION

Full Name_____ MD/DO/Other_____

Street _____

City _____ State _____ ZIP Code _____

PHYSICIANS: Are you licensed in the US? (circle) YES or NO

Email Address _____ @ _____

I certify that I completed this CME activity: The actual amount of time I spent in this activity was: _____hours _____minutes

Signature _____ Date Completed_____

The Dannemiller Memorial Educational Foundation would appreciate your comments regarding the quality of the information presented. Later, via email, we would also like to send you a website link to a follow-up survey regarding the material presented. May we contact you? (Please check one.)

___ Yes, via Email. ___ No, please do not contact me.

1. The program objectives were fully met.
   Strongly Agree Agree Disagree Strongly Disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.
   Strongly Agree Agree Disagree Strongly Disagree

3. The educational activity has enhanced my professional effectiveness to treat patients.
   Strongly Agree Agree Disagree Strongly Disagree NA

4. The educational activity will result in a change in my practice behavior.
   Strongly Agree Agree Disagree Strongly Disagree NA

5. The information presented was *without* promotional or commercial bias.
   Strongly Agree Agree Disagree Strongly Disagree

   (When answering this question, please refer to the following guidelines set forth by the ACCME regarding commercial bias and fair balance: *Discussion of commercial products must be free of bias for or against any one product and must present objective information about each product discussed: only generic names of therapeutic options should be used, however if trades names are used, those of several companies must be discussed in the activity.*)

6. Comments/suggestions regarding *this* material. _____

_____

7. Recommendations for topics of *future* presentations. _____

_____